

Figure 1

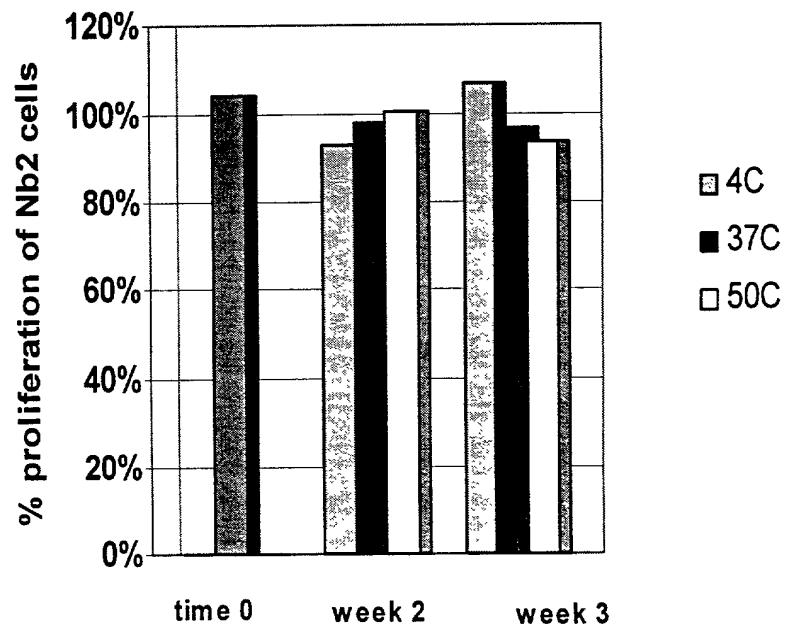


Figure 2

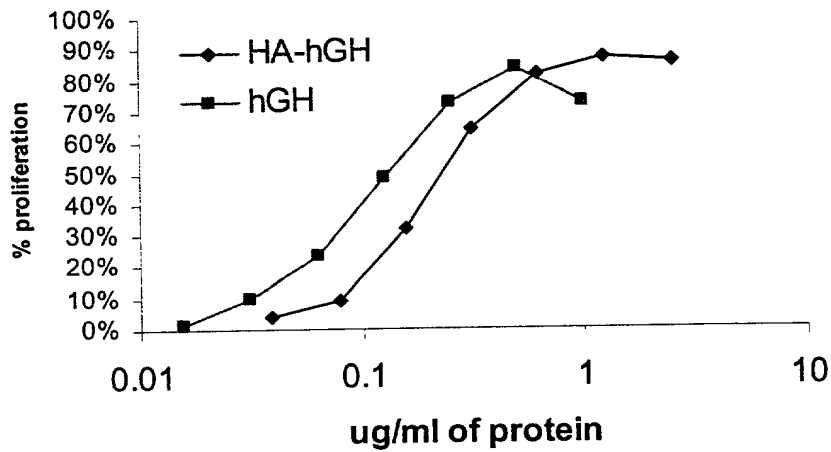


Figure 3A

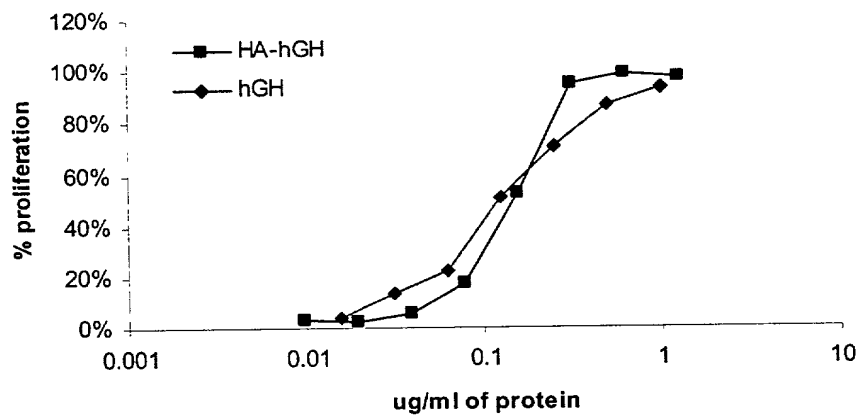


Figure 3B

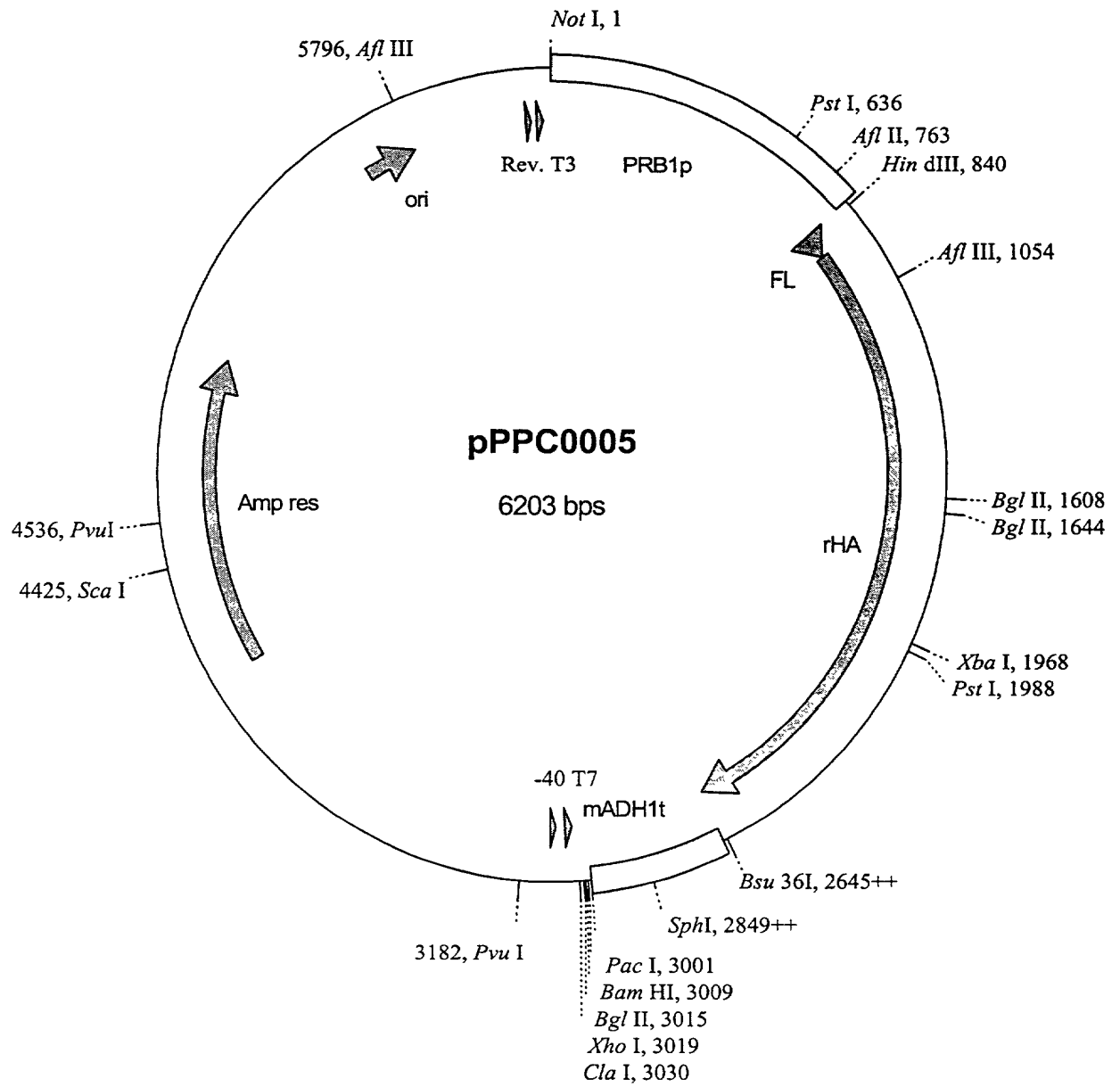


Figure 4

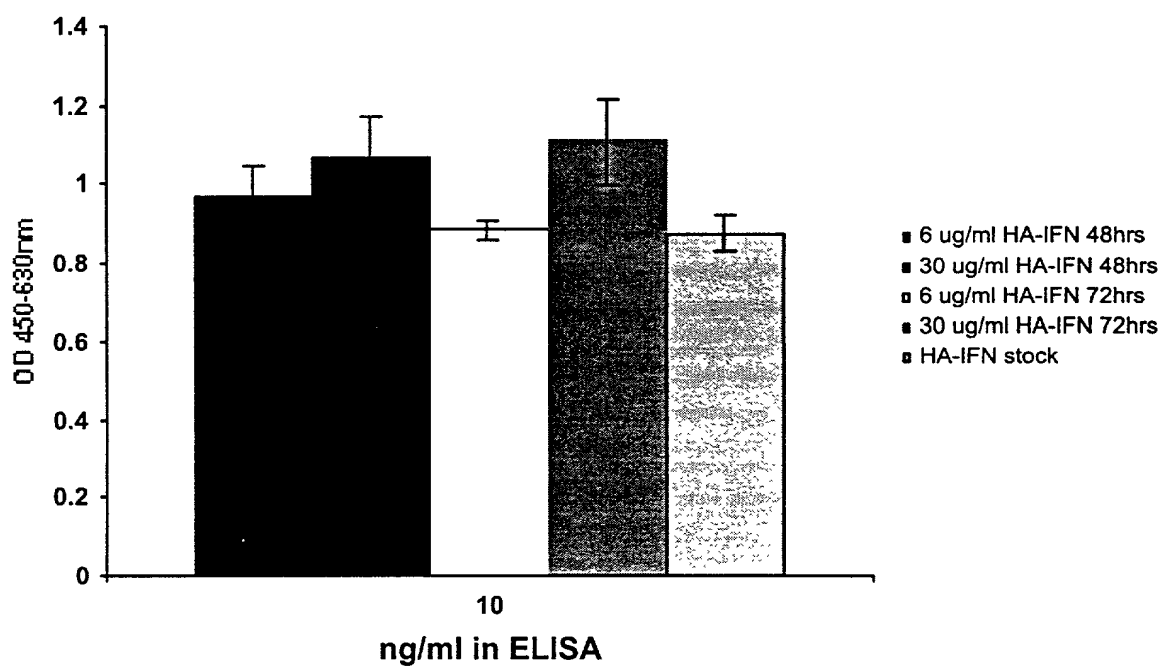


Figure 5

Figure 6

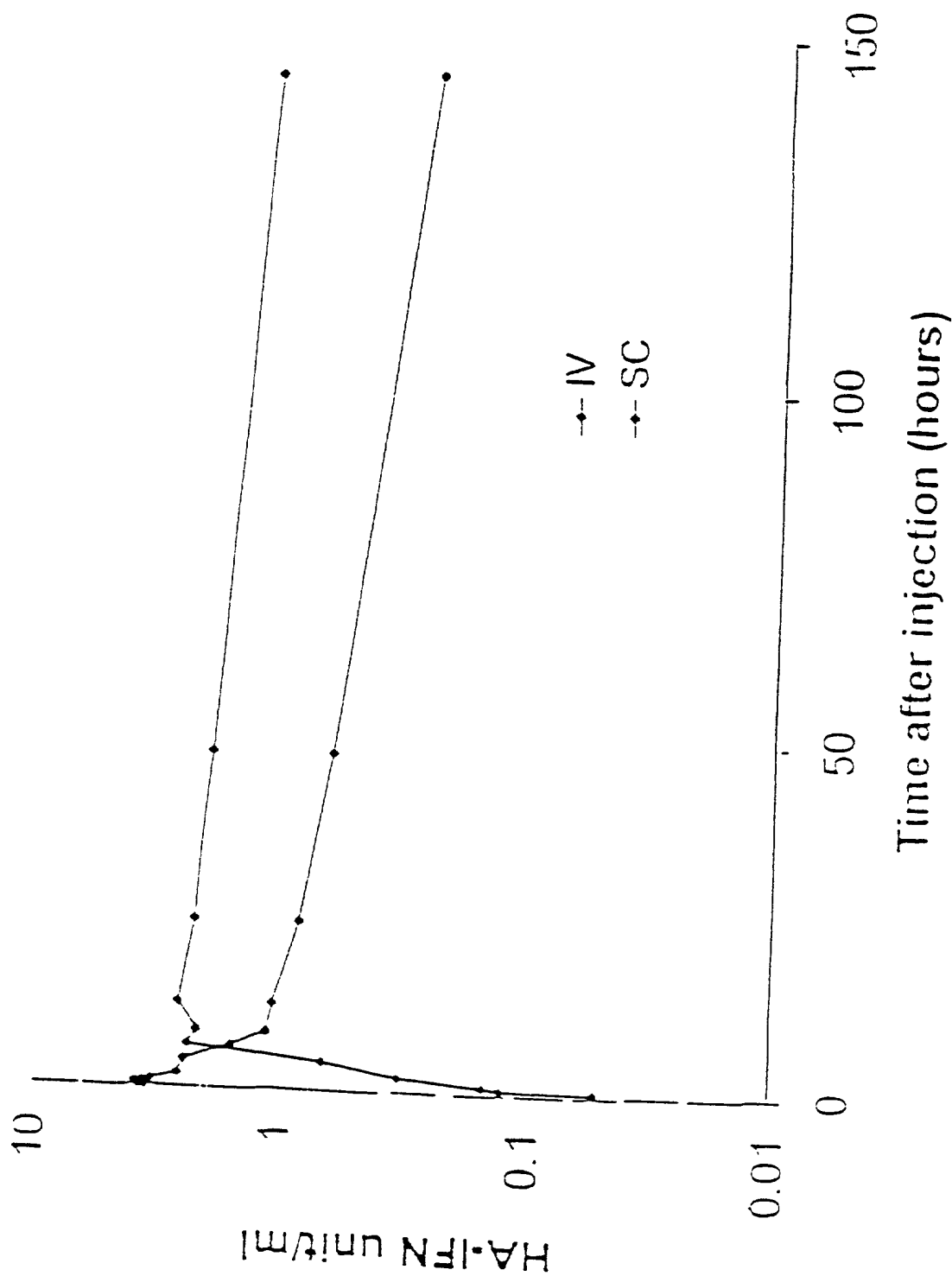
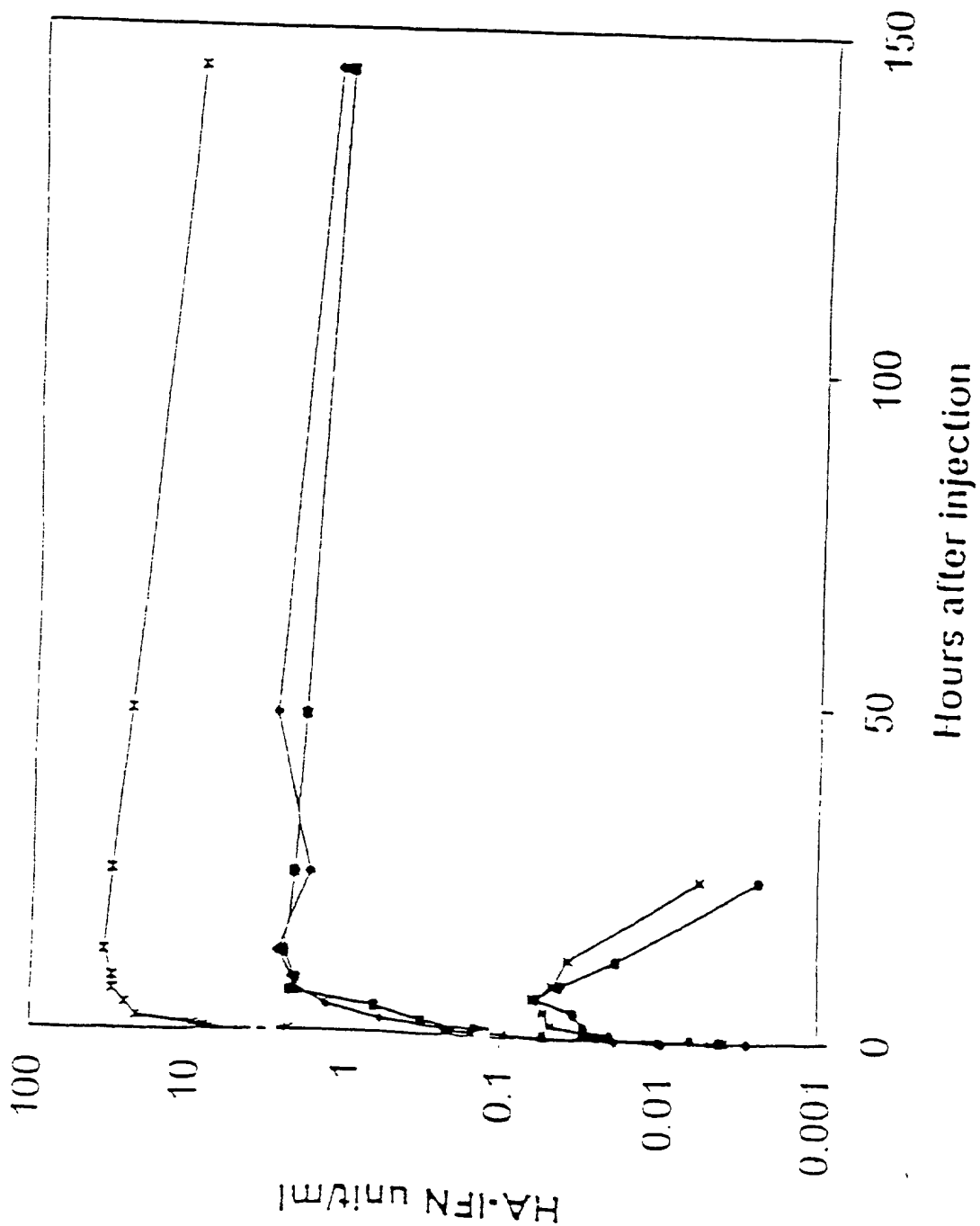


Figure 7



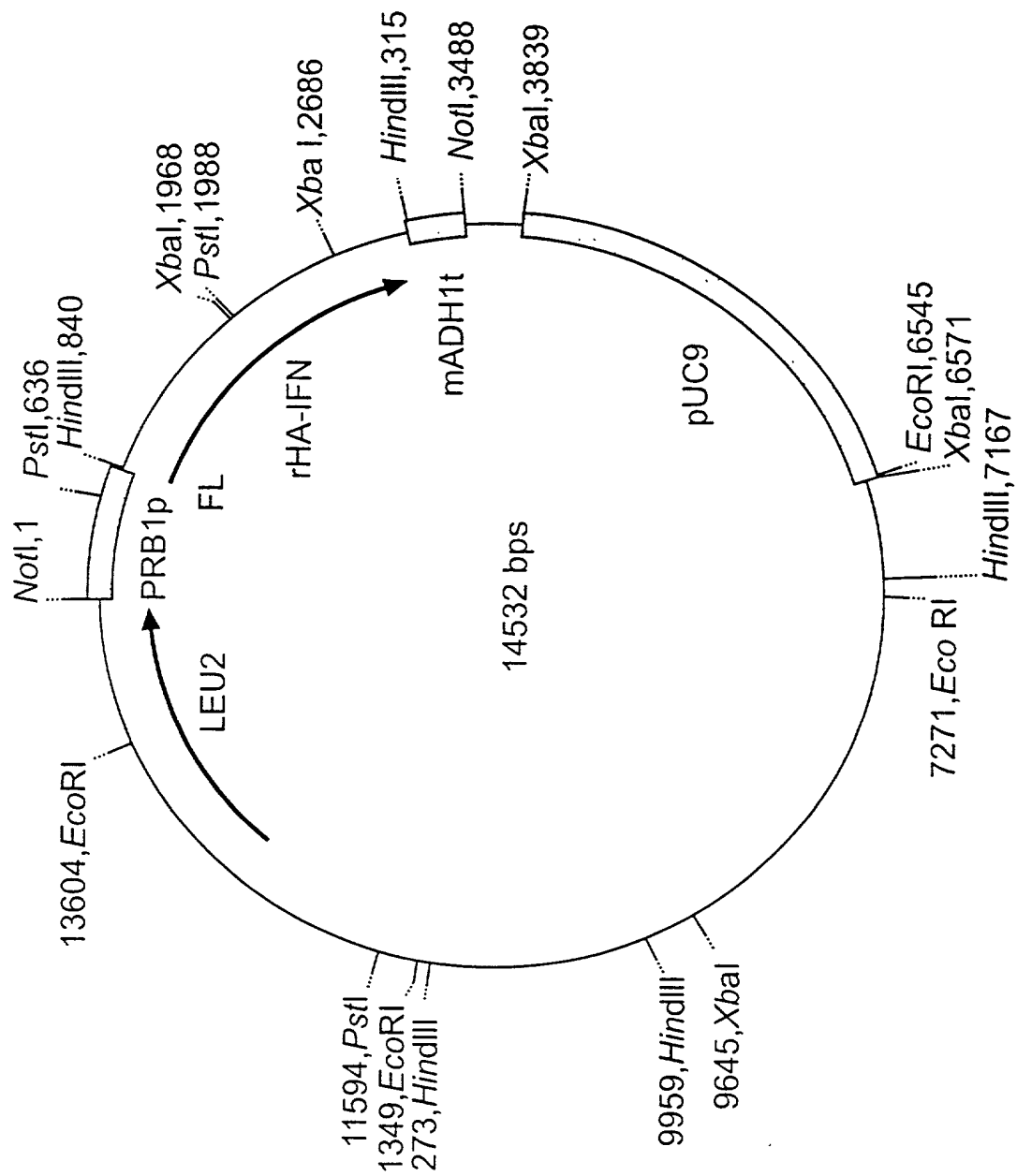


FIG. 8

Figure 9

1	DAHKSEVAHR	FKDLGEENFK	ALVLI AFAQY	LQCCPFEDHV	KLVNEVTEFA
	HHHHH	HHH	HHH	HHHHHHHHHH	HHHHH
					HHHHHHHHHH
	I			II	III
51	KTCV <u>ADESAE</u>	NCDKSLHTLF	GDKLC <u>TVATL</u>	RETYGEMADC	<u>CAKOE</u> PERNE
	HHHHH	HHHHH	HHHHH	HHHH	H
					HHHH
101	CFLQHKDDNP	NLPRLVRPEV	DVMCTAFHDN	EETFLKKYLY	EIARRHPYFY
	HHHH	H	HHHHHHHH	HHHHHHHHH	HHHHH
			IV		
151	APELLFFAKR	YKAAFTECCO	<u>AADKAA</u> CLLP	KLDEL RDEGK	ASSAKQRLKC
	HHHHHHHHHH	HHHHHHHHH	HHHHH	HHHEHHHHHH	HHHHHHHHHH
					V
201	ASLQKFGERA	FKAWAVARLS	QRFPKAEFAE	VSKLVTDLTK	VHTECC <u>HGDL</u>
	HHHHH	HH	HHH	HHHHHHHHHH	HHHHHH
					HH
		VI		VII	
251	<u>LECADDRADL</u>	AKYIC <u>ENODS</u>	<u>ISSKLKECCE</u>	<u>KPLLEKSHCI</u>	AEVENDEMPA
	HHHHHHHHHH	HHHHH	HHHHH	HHHHHHH	H
301	DLPSLAADFV	ESKDVCKNYA	EAKDVFLGMF	LYEYARRHPD	YSVVL LRLA
	HHHH	HHHHHH	HHHHHHH	HHHHHH	HHHHHHHH
		VIII			
351	KTYETTLEKC	<u>CAAADPHECY</u>	AKVFDEFKPL	VEEPQNLIKQ	NCELFEQLGE
	HHHHHHHHHH	HH	H	HHHHH	HHHHHHHHH
					HHHHHHH
					IX
401	YKFQNAL LVR	YTKKVPQVST	PTLVEVSRNL	GKVGSKCC <u>KH</u>	<u>PEAKRMP</u> CAE
	HHHHHHHHHH	HHHH	H	HHHHHHHHHH	HHH
					HHHHHHHH
		X		XI	
451	DYLSVVLNQL	<u>CVLHEKT</u> PVS	<u>DRVTKCCTES</u>	<u>LVNRRP</u> PCFSA	LEVDETYVPK
	HHHHHHHHHH	HHHHH	HHHHHHHHH	HHHHHHHH	
501	EFNAETFTFH	ADICTLSEKE	RQIKKQTALV	ELVKHKPKAT	KEQLKAVMDD
		HHH	HHH	HHHHHMEHHH	HHH
					HHHHHHHH
		XII			
551	FAAFVEKCKK	<u>ADDKET</u> CFAE	EGKKLVAASQ	AALGL	
	HHHHHHHHH	HHHH	HHHHHHHHHH	HH	

Loop

I	Val54-Asn61
II	Thr76-Asp89
III	Ala92-Glu100
IV	Gln170-Ala176
V	His247-Glu252
VI	Glu266-Glu277

Loop

VII	Glu280-His288
VIII	Ala362-Glu368
IX	Lys439-Pro447
X	Val462-Lys475
XI	Thr478-Pro486
XII	Lys560-Thr566

Figure 10

a. Randomisation of Loop IV.

151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

151 APELLFFAKR YKAAFTECCX XXXXXXCLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

b. Insertion (or replacement) of Randomised sequence into Loop IV.

(X)_n
 ↓
 151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.

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TO FIG. 11B

FIG. 11A



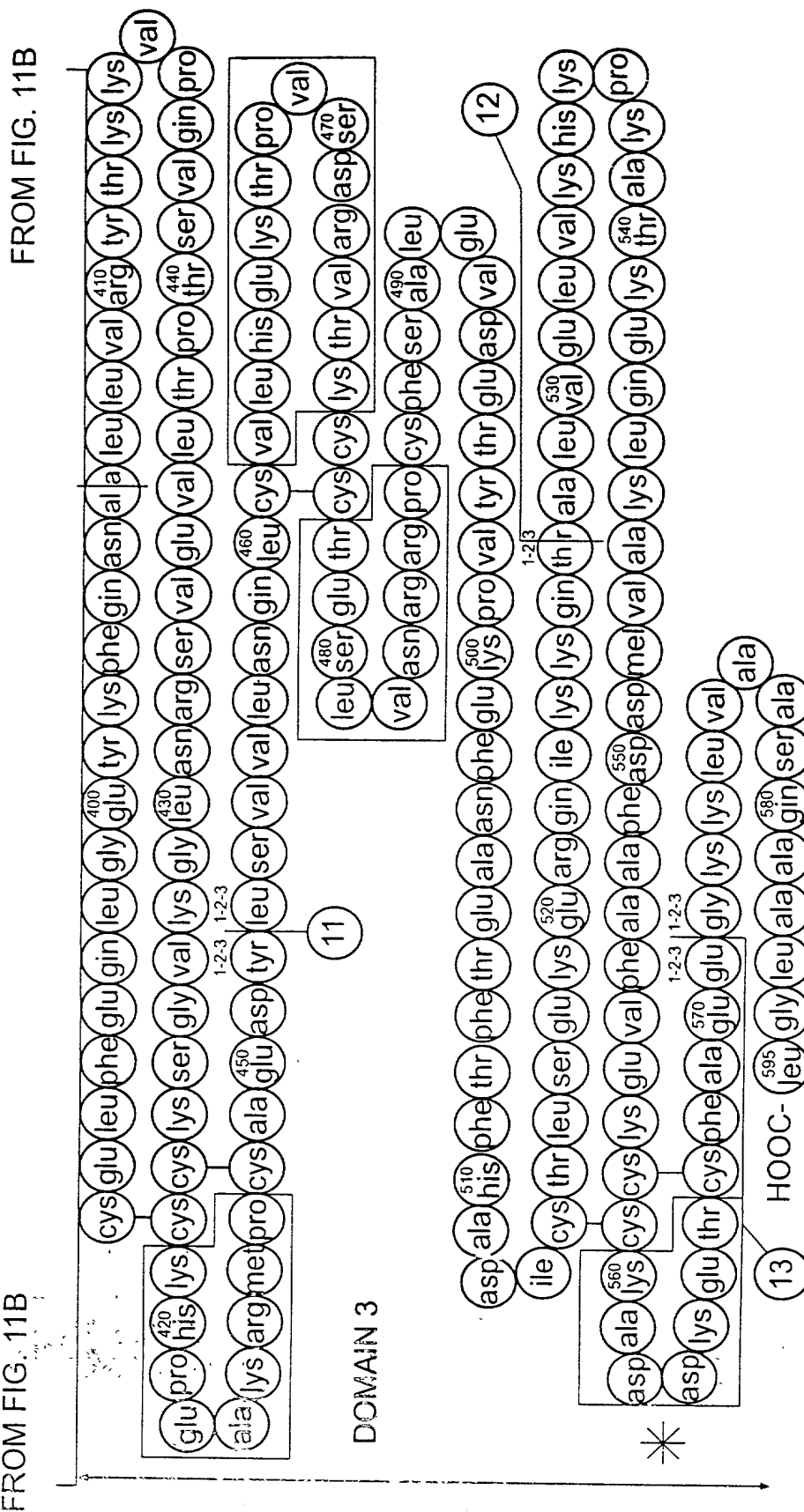


FIG. 11C

TO:230" TFE860



DISULFIDE BONDS SHOWN IN YELLOW

FIG. 12:
LOOP IV GLU170-A176

102230" TTEE860

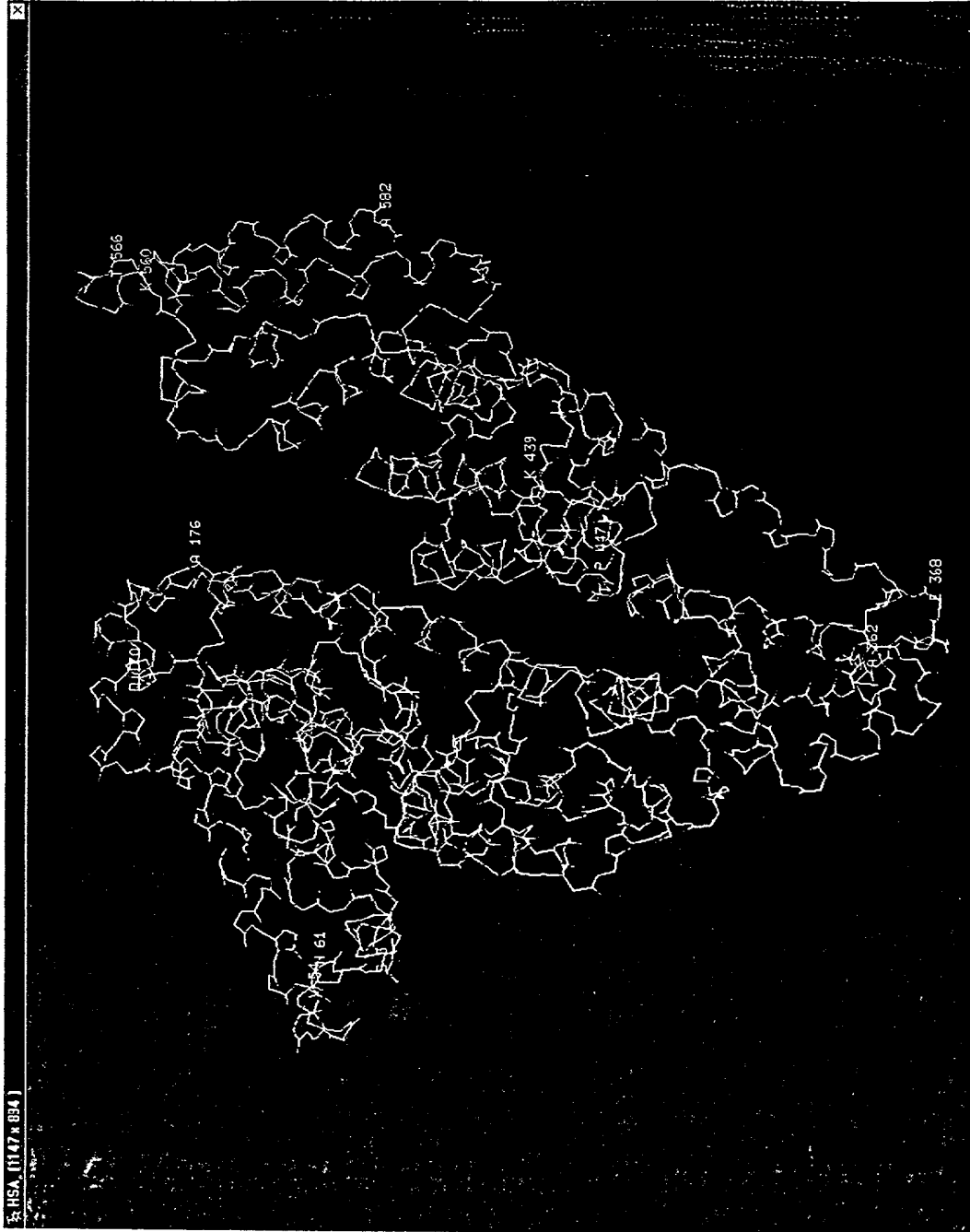


FIG. 13
TERTIARY STRUCTURE OF HA

FO/280" TTFEEB6D

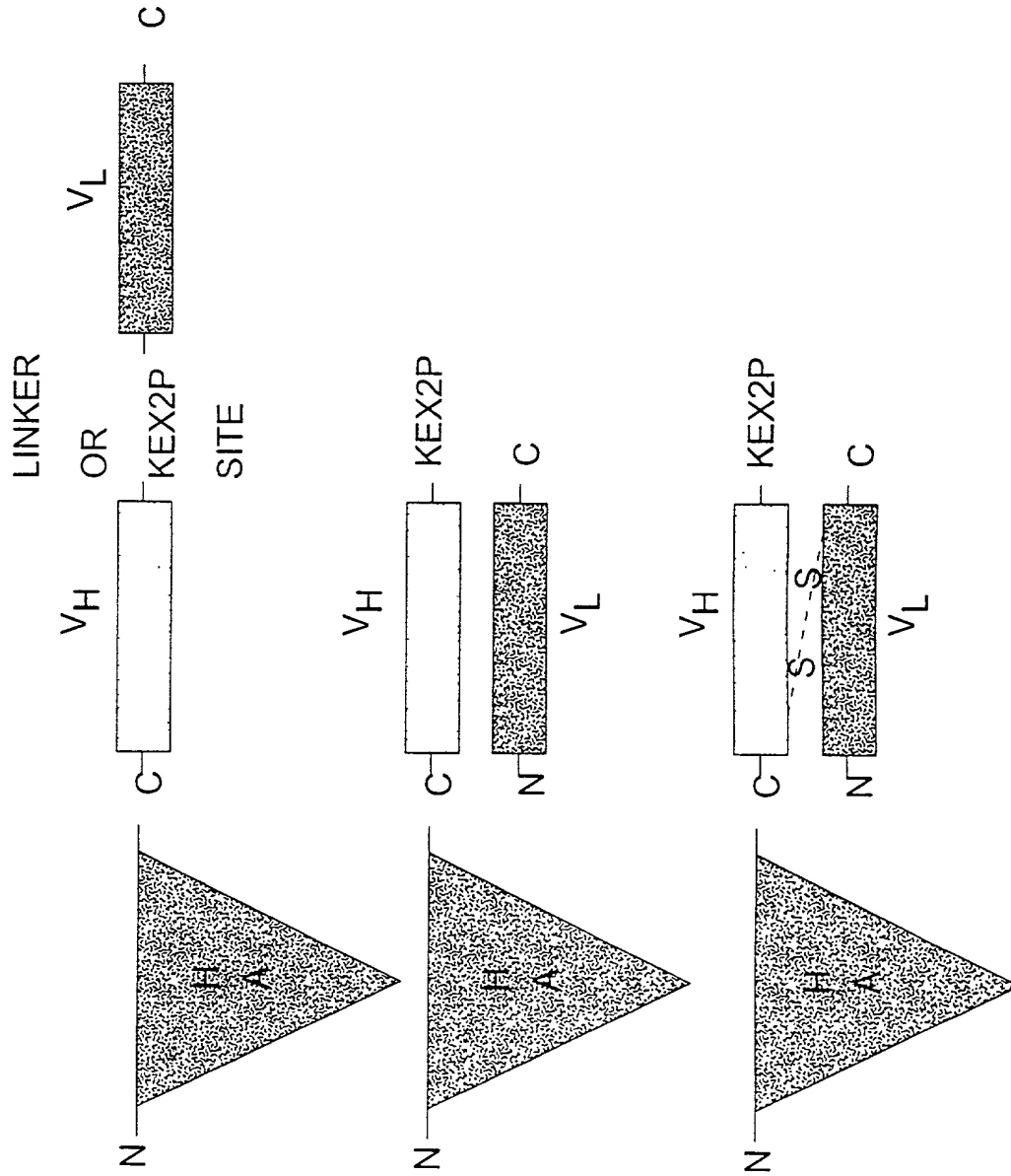


FIG. 14

TTTGGGAAATTTCTT

1 GAT GCA CAC AAG ACT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA AAT TTC AAA 60
 1 D A H K S E V A H R F K D L G E E N F K 20

61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A L V L I A F A Q Y L Q Q C P F E D H V 40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
 41 K L V N E V T E F A K T C V A D E S A E 60

181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N C D K S L H T L F G D K L C T V A T L 80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R E T Y G E M A D C C A K Q E P E R N E 100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
 101 C F L Q H K D D N P N L P R L V R P E V 120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
 121 D V M C T A F H D N E E T F L K K Y L Y 140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
 141 E I A R R H P Y F Y A P E L L F F A K R 160

Figure 15A

TTTGGG

481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
 161 Y K A A F T E C C Q A A D K A A C L L P 180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
 181 K L D E L R D E G K A S S A K Q R L K C 200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
 201 A S L Q K F G E R A F K A W A V A R L S 220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
 221 Q R F P K A E F A E V S K L V T D L T K 240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780
 241 V H T E C C H G D L L E C A D D R A D L 260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
 261 A K Y I C E N Q D S I S S K L K E C C E 280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
 281 K P L L E K S H C I A E V E N D E M P A 300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
 301 D L P S L A A A D F V E S K D V C K N Y A 320

Figure 15B

Figure 15C

1002280 "TTTCC360"

```
1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
481 L V N R R P C F S A L E V D E T Y V P K 500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
501 E F N A E T F T F H A D I C T L S E K E 520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
521 R Q I K K Q T A L V E L V K H K P K A T 540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
541 K E Q L K A V M D D F A A F V E K C C K 560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
561 A D D K E T C F A E E G K K L V A A S Q 580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
581 A A L G L * 585
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Figure 15D